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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,814	07/26/2001	Madeline M. Butler	ISPH-0587	6393

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EXAMINER
ZARA, JANE J

ART UNIT	PAPER NUMBER
1635	8

DATE MAILED: 01/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary

Application No.	Applicant(s)
09/915,814	Butler et al
Examiner	**Art Unit**
Jane Zara	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Nov 1, 2002* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, and 4-71* is/are pending in the application.

4a) Of the above, claim(s) *16-70* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-15, and 71* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1,2, 4-71 are pending in the instant application.

Election/Restriction

Applicant's election with traverse of Group I, claims 1, 2, 4-15 and 71, and SEQ ID NO: 3 in Paper No.7 is acknowledged. The traversal is on the ground(s) that the all of the claims relate to the single concept of modulating expression of hormone sensitive lipase, that the various antisense sequences claimed comprise a single invention because they are all subsequences of the same target molecule, and that searching all the antisense sequences claimed would not impose an undue burden onto the examiner. These arguments are not found persuasive because various methods claimed concern treatment of distinct and different diseases and conditions, and a proper examination of the various inventions, including modulating blood glucose levels, modulating serum cholesterol levels, modulating serum triglyceride levels, and delaying diseases associated with hormone sensitive lipase expression, involves addressing different and distinct art and enablement issues. Furthermore, each antisense sequence claimed is a distinct and separately patentable invention, despite the fact that all the sequences are subsequences of a single, common target molecule. In addition, searching the appropriate data bases for all of the antisense sequences and all of the methods claimed would present an undue burden on both the examiner and the existing search facilities.

The requirement is still deemed proper and is therefore made FINAL.

The amendment filed on November 1, 2002 in response to the election requirement mailed October 3, 2002 has been acknowledged. Applicant timely traversed the restriction (election) requirement in Paper No. 7 .

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 11, line 3, the term "active site" is vague and unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 71 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to compositions for specifically targeting and inhibiting the expression of any and/or all alternatively spliced forms of (human) hormone sensitive lipase (hsl). The

specification and claim do not describe elements which are essential to the claimed invention, which elements include the sequences of any and/or all alternatively spliced forms of hsl. The scope of the claim includes structural variants and concise structural features that identify structures within the genus comprising alternatively spliced forms of hsl are missing from the disclosure. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. The specification fails to teach or adequately describe the characteristics concisely identifying members of the proposed genus and the description provided is insufficient. One of skill in the art would reasonably conclude that the disclosure fails to provide an adequate description of the genus claimed. Thus, Applicant was not in possession of the claimed genus.

Claims 15 and 71 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the in vitro inhibition of human hormone sensitive lipase (hsl) comprising the administration of antisense oligonucleotides, does not reasonably provide enablement for the in vivo inhibition of hsl comprising the administration (by any and/or all routes of administration) of antisense, nor for any and/or all compounds that hybridize with and inhibit the expression of nucleic acids encoding any and/or all alternatively spliced forms of hsl. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are drawn to compositions and methods for inhibiting the expression of hsl encoded by SEQ ID NO: 3, and/or any alternatively spliced forms of hsl in vitro or in vivo, comprising the administration of antisense oligonucleotides between 8-50 nucleobases which specifically target hsl, or any alternatively spliced forms of hsl.

The following factors have been considered in determining that the specification does not enable the skilled artisan to make and/or use the invention over the scope claimed.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate the state of the art of antisense treatment in organisms. Branch and Crooke teach that the in vivo (whole organism) application of nucleic acids (such as antisense) is a highly unpredictable endeavor due to target accessibility and delivery issues. Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target genes. (See entire text for Branch and especially pages 34-36 for Crooke). The high level of unpredictability regarding the prediction of antisense efficacy in treating disease states was illustrated in the clinical trial results obtained by ISIS pharmaceuticals for the treatment of Crohn's disease using antisense targeting ICAM-1, whereby the placebo treatment was found more successful than antisense treatment (BioWorld Today: See entire article, especially paragraphs 3 and 5-7 on page 1). Additionally, Palu et al teach that the success of gene delivery using virally derived vectors is dependent on the empirical determination of successful gene transduction for a given vector and a given target cell (See entire article, especially page 4, section 2.). Agrawal et al speak to the unpredictable nature of the antisense field thus: "It is therefore

appropriate to study each antisense oligonucleotide in its own context, and relevant cell line, without generalizing the results for every oligonucleotide." (see page 80). Cellular uptake of antisense oligonucleotides by appropriate target cells is another rate limiting step that has yet to be overcome in achieving predictable clinical efficacy using antisense. Both Chirila et al and Agrawal et al point to the current limitations which exist in our understanding of the cellular uptake of antisense oligonucleotides in vitro and in vivo (see Agrawal et al especially at pages 79-80; see Chirila et al in its entirety, especially pages 326-327 for a general review of the "important and inordinately difficult challenge" of the delivery of therapeutic antisense oligonucleotides to target cells).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. Applicants have not provided guidance in the specification toward a method of inhibiting hsl and any and/or all alternatively spliced forms of hsl in vitro or in vivo comprising the administration of antisense, via any and/or all routes of administration.

The specification teaches the inhibition of hsl encoded by SEQ ID NO: 3 in vitro and in vivo (via intraperitoneal administration) comprising the administration of antisense oligonucleotide ISIS 126930. The specification fails to teach the inhibition of hsl expression, or the specific targeting and inhibition of expression of any and/or all alternatively spliced forms of hsl in vitro or in vivo, comprising the administration (by any and/or all routes of administration) of antisense between 8-50 nucleobases. One skilled in the art would not accept on its face the

examples given in the specification of the in vitro and in vivo (via intraperitoneal administration) targeting and inhibition of hsl encoded by SEQ ID NO: 3, using antisense oligonucleotide ISIS 126930 as being correlative or representative of the successful inhibition of hsl and any and/or all alternatively spliced forms of hsl in vitro or in vivo, via any and/or all routes of administration, in view of the lack of guidance in the specification and known unpredictability associated with successful targeting and inhibition using antisense in vivo, as well as a lack of guidance for the identification and successful inhibition of any and/or all alternatively spliced forms of hsl in vitro or in vivo. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery (by any and/or all routes of administration) and inhibition of expression of a particular target molecule by antisense administered, and specifically regarding expression of nucleic acids encoding hsl of SEQ ID NO: 3, or any and/or all alternatively spliced forms of hsl.

The breadth of the claims and the quantity of experimentation required. The breadth of the claims is very broad. The claims are drawn to compositions and methods for inhibiting the expression of hsl-3 in vitro or in vivo, or any and/or all alternatively spliced forms of hsl, comprising the administration by any route of antisense oligonucleotides between 8-50 nucleobases. The quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues harboring the target molecule hsl, as well as any and/or all alternatively spliced forms of hsl in vitro or in vivo, whereby hsl expression is inhibited in vitro

and vivo. Since the specification fails to provide any particular guidance for the identity and inhibition of expression of any and/or all alternatively spliced forms of hsl in vitro or in vivo, or for the inhibition of hsl expression in an organism comprising the administration (by any and/or all routes of administration) of antisense, and since determination of the factors required for in vivo success of any and/or all alternatively spliced forms of hsl is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 4-8, 11-15 are rejected under 35 U.S.C. 102(a) as being anticipated by Mitchell et al.

Mitchell et al (document "AA" provided in the IDS, filed October 19, 2001, Paper No. 4) teach compositions comprising antisense oligonucleotides between 8-50 nucleobases which specifically target and inhibit the expression of SEQ ID NO: 3 in vitro, and which antisense comprise phosphorothioate internucleotide linkages, 2'-O methoxyethyl sugars, and modified

nucleobases, and which compositions further comprise a pharmaceutically acceptable carrier and a colloidal dispersion system (See entire document, especially page 4, pages 6-8, pages 11-13, and the accompanying sequence alignment data).

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Holst et al.

Holst et al teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3 (See especially the fourth full paragraph on page 442).

Claims 1 and 2 are rejected under 35 U.S.C. 102(b) as being anticipated by Langin et al.

Langin et al teach antisense oligonucleotides between 8-50 nucleobases which target and inhibit the expression of SEQ ID NO: 3 (See especially second and fourth full paragraphs on page 4898).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitchell et al, Holst et al and Langin et al as applied to claims 1, 2, 4-8, 11-14 above, and further in view of Baracchini et al.

The claims are drawn to compositions comprising antisense oligonucleotide compounds between 8-50 nucleotides which specifically target and inhibit the expression of human hsl of SEQ ID NO: 3 in vitro, and which oligonucleotides further comprise internucleotide linkage modifications, sugar modifications, a 5-methyl cytosine nucleobase modification, and may optionally comprise a chimeric oligonucleotide, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system.

Mitchell et al, Holst et al and Langin et al are relied upon as stated in the 102 rejections above. These primary references do not teach chimeric oligonucleotides, nor 5'-methyl cytosine modified nucleobases.

Baracchini et al teach the incorporation 5 methyl cytosines and chimeric structures into antisense oligonucleotides for enhancing target binding, cellular uptake and stability of antisense oligonucleotides (see col. 7-8).

It would have been obvious to one of ordinary skill in the art to incorporate various modifications into antisense such as internucleotide linkage, nucleobase, or sugar modifications, as well as designing chimeric antisense oligonucleotides, because Baracchini and Mitchell et al had taught previously that such modifications contribute to the stability, cellular uptake and target binding of antisense oligonucleotide compounds. One of ordinary skill in the art therefore would have expected that antisense comprising such modifications would exhibit enhanced stability, cellular uptake and target binding. One of ordinary skill in the art would have been motivated to utilize compositions comprising pharmaceutically acceptable diluents and colloidal dispersion

systems, in combination with antisense oligonucleotides, for transfecting target cells because such compositions had been taught previously by Baracchini et al and one would have expected that such compositions would minimize toxic effects of target cells while enhancing cellular uptake of the antisense oligonucleotides. Therefore, the invention has a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (703) 308-0447. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (703) 305-3413. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A Lacourciere

KAREN LACOURCIERE
PATENT EXAMINER

JZ

January 10, 2003